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U.S. Environmental Protection Agency
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

Sufficient data are not available at this time on asbestos to determine either acceptable intakes or q_1^*s.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with asbestos. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Asbestos. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA-440/5-80-022. NTIS PB 81-117335.

U.S. EPA. 1983a. Reportable Quantity for Asbestos. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Review of Toxicologic Data in Support of Evaluation of Carcinogenic Potential of Asbestos. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983c. Technical Support Document on the Ranking of Hazardous Chemicals Based on Carcinogenicity. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Asbestos. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983d).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Human data clearly indicate that asbestos exposure from inhalation contributes to excess risk for GI and lung cancer, and peritoneal mesothelioma data in animals are corroborative. Evidence for the carcinogenicity of asbestos following oral exposure is equivocal. Since the carcinogenic potency of asbestos appears to be dependent upon fiber size and shape, a carcinogenic potency estimate for "generic" asbestos is not proposed at this time.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BaP	Benzo(a)pyrene
bw	Body weight
CHO	Chinese hamster ovary
CS	Composite score
GI	Gastrointestinal
TEM	Transmission electron microscope
TLV	Threshold limit value
TWA	Time-weighted average
UICC	International Union Against Cancer

1. ENVIRONMENTAL CHEMISTRY AND FATE

Asbestos is a generic term applied to a variety of naturally formed hydrated silicates containing metal cations such as sodium, magnesium, calcium or iron. The two major groups of asbestos are serpentine and amphibole. Chrysotile is the only form of asbestos that belongs to the serpentine group. The amphibole group exists in five different classes: actinolite, amosite, anthophyllite, crocidolite and tremolite. Only chrysotile, amosite, crocidolite and anthophyllite are of commercial importance (IARC, 1973), and the first three varieties constituted a total of 99.9% of asbestos production in 1976 (Streib, 1978). A few selected physical and chemical properties of chrysotile, amosite and crocidolite asbestos are shown in Table 1-1.

Of the 243,527 metric tons of asbestos discharged to the environment, ~1.5% is discharged in the air (U.S. EPA, 1980b). Based on its lack of reactivity in aquatic media (Callahan et al., 1979), it is not likely that asbestos will undergo any photochemical reaction or other chemical reactions in air. Both rainouts and dry deposition may be primarily responsible for the removal of asbestos from air. The lifetime of particulate matter for the physical removal mechanism is dependent on the particle size. The exact particle size distribution of atmospheric asbestos is unknown, but it is known that only a small fraction of atmospheric asbestos has particle lengths of >5 μm (U.S. EPA, 1980b). Based on the half-life of other atmospheric metals (although the particle shape may be different from that of asbestos), it is speculated that the half-life of submicron asbestos particles may be several days. The aquatic fate of asbestos has been discussed by Callahan et al. (1979). It appears from this report that asbestos

TABLE 1-1

Selected Physical and Chemical Properties of Asbestos[a]

Property	Asbestos Form		
	Chrysotile	Amosite	Crocidolite
CAS No.	12001-29-5	12172-73-5	12001-28-4
Idealized formula	$Mg_3Si_2O_5(OH)_4$	$(Fe^{+2}Mg)_7Si_8O_{22}(OH)_2$	$Na_2Fe_3^{+2}Fe_2^{+3}Si_8O_{22}(OH)_2$
Specific gravity	2.55	3.43	3.37
Approximate diameter of smallest fibers (μm)[b]	0.01	0.1	0.08
Maximum solubility in HCl: % loss in weight	56.0	12.0	3.14
Maximum solubility in NaOH: % loss in weight	1.03	6.82	1.20
Electric charge	positive	negative	negative

remains chemically inert in the aquatic environment. The only significant mechanism of asbestos transfer from aquatic phase to sediment is through coagulation of asbestos or other processes of precipitation such as adsorption through clay and subsequent precipitation. Although the estimated half-life of asbestos in the aquatic system is not known, it is expected to be quite long.

Limited information regarding the fate of asbestos in soil is available in the literature. Based on its predicted inability to undergo chemical reactions, degradation and volatilization from water (Callahan et al., 1979), none of these reactions are expected to be significant in soil. Based on its solubility in acidic and basic media, leaching of asbestos from soils is possible; however, the leaching process may destroy the crystalline structure of asbestos by solubilizing the element in the asbestos structure.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

The weight of evidence suggests that the toxicity and carcinogenicity of asbestos are associated with the nature of the asbestos fibers and their actions upon the cells with which they come in contact or penetrate. Since asbestos fibers are neither water nor lipid soluble, it seems unlikely that absorption of asbestos fibers takes place either by passive diffusion or active transport, but more likely as a result of the fibers mechanically penetrating a tissue barrier, such as the epithelial lining of the GI tract (persorption). Phagocytosis of asbestos fibers by macrophages, monocytes or other phagocytic cells is probably involved in absorption, or uptake, and subsequent distribution of asbestos fibers to other tissues, including the lymphatic system or the bloodstream, resulting in widespread body distribution.

The evidence for GI uptake of asbestos fibers in humans is highly suggestive, but not absolutely conclusive. Fibers of amphibole asbestos (not otherwise specified) were discovered in Duluth, MN, drinking water (Carter and Taylor, 1980). The presence of amphibole fibers, which resembled those found in the drinking water, were demonstrated in the liver, jejunum and lung specimens from deceased Duluth residents. Among 96 tissue specimens from 32 deceased Duluth residents, amphibole fibers were found in 60, with concentrations ranging from $3\text{-}16 \times 10^5$ fibers of all sizes/g of tissue. A control cohort consisted of 61 tissue specimens from 21 deceased residents of Houston, TX, and St. Paul, MN. Amphibole fibers were found in only two tissue specimens in the control cohort. Since air sampling gave no evidence of amphibole air concentrations in Duluth, these authors concluded that the

presence of amphibole fibers in these tissues indicated transmucosal uptake of fibers resulting from ingestion of amphibole-contaminated drinking water in Duluth, MN.

Cook and Olson (1979) examined the urine sediment from humans who ingested drinking water in Duluth, MN, contaminated with amphibole asbestos fibers. Measured concentrations of amphibole fibers eliminated in the urine averaged ~$1x10^{-3}$ times the concentration of amphibole fibers in the drinking water. The authors noted that applying adequate filtration to the drinking water removed the amphibole fibers and resulted in a gradual disappearance of amphibole fibers from the urine. They concluded that these observations provided direct evidence of the passage of asbestos fibers through normal human GI mucosa. Furthermore, they emphasized that, since some body retention of asbestos fibers undoubtedly occurs, urinary concentrations of asbestos are an underestimation of the actual uptake of asbestos.

Boatman et al. (1983) discovered that drinking water in the Puget Sound area had unusually high levels of asbestos, with tap water from the homes of seven individuals containing 230-383x10^6 chrysotile fibers/ℓ. A control group consisted of four residents from the Seattle/Bellevue area whose tap water contained 1.2-3.1x10^6 chrysotile fibers/ℓ. The content of chrysotile fibers in the urine of long-term ($\geq$24 years) residents of the Puget Sound area was significantly ($p=0.05$) higher than the content of chrysotile fibers in the urine of short-term (1.5-2.8 years) residents. There was no significant difference, however, in the urinary content of chrysotile for Puget Sound compared to that from the Seattle/Bellevue residents. These authors, however, reported some difficulties with their Nucleopore membrane filters, which may have resulted in the lack of statistically significant data generated in this study.

In animals, a substantial body of evidence also exists that is highly suggestive of GI uptake of asbestos fibers, but some investigators doubt that this phenomenon occurs. An early investigation indicated that fiber uptake across the GI lining did not occur (Gross et al., 1974), but this conclusion has been challenged by Cooper and Cooper (1978), who questioned the sensitivity of the analytical procedure used.

Following ingestion of chrysotile or amosite asbestos by rats, fibers have been found in the colonic mucosa (Westlake et al., 1965) or penetrating the epithelial cells of the jejunal mucosa (Storeygard and Brown, 1977). Kidney cortical tissue of a neonatal baboon fed chrysotile for 9 days was found to contain a significant ($p=0.005$) excess of chrysotile fibers compared to the kidney cortical tissue from an untreated neonatal baboon (Patel-Mandlik and Hallenbeck, 1978).

Patel-Mandlik and Millette (1983a,b) treated 20 Sprague-Dawley rats with 50 mg chrysotile asbestos/kg by gavage 2 times/week until natural death or sacrifice. A control group of rats was maintained. The test group of 20 rats was further divided into four groups of five rats, depending on age at death or sacrifice. The four groups consisted of rats from <200, 200-400, 400-600 or >600 days of age when examined. There was a significant ($p<0.005$) difference in the kidney cortical content of chrysotile between the different treatment groups of rats, but the difference did not correlate with duration of treatment. There was also a significant difference ($p<0.005$) between the kidney cortical content of chrysotile in treatment rats (1.15 fibers/TEM grid) compared with control rats (0.05 fibers/TEM grid).

Following pretreatment, dietary regimens of 0 or 50 mg/day of UICC chrysotile A for 30 days, male MRC-hooded rats were given single oral doses of 50, 30 or 1 mg or 10 or 0.1 μg of UICC chrysotile A or "prepared" chrysotile (>90% of fibers <5 μm in length) (Weinzweigh and Richards, 1983). Control rats were maintained. The portal hepatic vein was ligated and blood samples were drawn for analysis of chrysotile at 2, 7 and 12 hours after the single oral dose of asbestos. The occurrence of chrysotile fibers in the blood from control rats complicated interpretation of the results. Peak levels of chrysotile in the blood seemed to occur ~7 hours after the single oral dose was administered. In 6 of the 15 trials, the level of chrysotile in the blood of treated rats was significantly greater than that of controls. Fibrils detected in blood were of small size (97% <1 μm). These authors suggested that migration of larger asbestos particles probably does not occur as a result of uptake into the portal circulation.

Cunningham et al. (1977) fed diets containing 1% chrysotile asbestos (22%, 0.3-1.0 μm; 59%, 1.1-3.0 μm; 9%, 3.1-5.0 μm; 10%, 5.1-10 μm; 10%, 10.1-50.0 μm) to 20 male Wistar rats for 6 weeks. To reduce dust and the likelihood of inhalation of asbestos, corn oil or molasses was added to the diet. Control rats were maintained. The rats were killed and tissues were examined; the results are summarized in Table 2-1. In treated rats, the greatest tissue content of chrysotile was observed in the omentum, followed by the brain and lungs. The fact that growth depression occurred in all treated groups implied that 1% chrysotile in the diet "had some biological effect." Food intake figures were not reported.

TABLE 2-1

Asbestos Levels in Rats Fed 1% Asbestos for 6 Weeks
(fibers x 10^6/g)[a]

Tissue	Controls	Asbestos Treated
Blood	0.00	0.57 ± 0.43
Omentum	1.08 ± 0.58	9.66 ± 3.18[b]
Lung	0.29 ± 0.08	1.02 ± 0.20[c]
Kidney	0.17 ± 0.03	0.36 ± 0.03[c]
Liver	0.13 ± 0.06	0.62 ± 0.30
Brain	0.22 ± 0.11	1.25 ± 0.34[b]

[a]Source: Cunningham et al., 1977

[b]$p<0.02$ using a t-test with each figure representing the average with standard error for 10 rats.

[c]$p<0.01$

Meek (1983), however, reported that no evidence for intestinal mucosal uptake could be found in rats treated with amosite. This investigator injected a 0.1 mℓ suspension of amosite in physiological saline into the wall of the intact GI tract of male Wistar rats to characterize the granulomatous changes expected as a result of amosite uptake. Dense accumulations of macrophages were observed in the injection site as a result of the injected amosite. Subsequently, other rats were treated by gavage with 100 mg UICC amosite for 5 days and then killed; their intestinal tracts were microscopically examined for the macrophagic invasion that was found to characterize the response to amosite. A lack of evidence of a macrophagic response or other pathological changes in the small intestine of treated rats was interpreted to mean that the "gut wall of rats may present an effective barrier to the penetration of asbestos...." Meek (1983) acknowledged the limitations of this study and suggested that further studies should involve electron microscopy of the mucosal cells.

According to Bolton et al. (1982), electron microscopic examination of the intestinal mucosa of male HAN spf Wistar rats exposed to asbestos failed to reveal any evidence of penetration or damage to gut tissues. Exposure was to UICC amosite, UICC crocidolite or UICC chrysotile A, at levels of 5 mg/g of margarine which was fed ad libitum for at least 25 months. Consumption of asbestos was ~250 mg/week. The result of the electron microscopic examination of tissue residues indicated no widespread penetration and/or dissemination of asbestos fibers in treated rats.

2.2. INHALATION

Comparatively few data have been located on the absorption of asbestos following inhalation exposure. Whether inspired asbestos fibers will be deposited in the lung depends strongly upon their diameter. Timbrell (1965)

has shown that a fiber, independent of its length, behaves aerodynamically like a particle having a diameter 3 times as great as its actual diameter. Brain and Valberg (1974) indicated that 50% of particles with a median diameter of <0.1 μm will be deposited on nonciliated pulmonary surfaces, as determined by a model for aerosol deposition based on the aerodynamic characteristics of particles. About 25% of particles with a diameter of 1 μm and 0% of particles with a diameter of 10 μm would be expected to deposit on nonciliated respiratory epithelium. Once inhaled, a large fraction of the inhaled fibers is rapidly cleared by mucociliary action, although some fibers will remain in the lung and can be found there decades after exposure (Pooley, 1973; Langer, 1974). Particularly large fibers trapped in the lungs may become coated or calcified and form asbestos bodies.

The clearance of asbestos from the respiratory tract of rats has been studied directly in a series of experiments (Morgan et al., 1975; Evans et al., 1973). Rats were exposed for 30 minutes to different varieties of UICC standard asbestos samples, made radioactive by neutron bombardment, and deposition and clearance from the respiratory tract was determined. Subsequently, distribution among various tissues of the body was measured. The results are presented in Table 2-2. These data indicate the magnitude of mucociliary clearance of asbestos fibers from the lungs.

A difference in the pulmonary retention of various forms of asbestos in Wistar rats exposed to 10.1-10.6 mg/m^3 for 7 hours/day, 5 days/week for 24 months was reported by Wagner et al. (1974). These authors determined that the amphiboles studied (amosite, anthrophyllite and crocidolite) accumulated in the lungs ~7 times as heavily as the two chrysotiles (a Canadian and a Rhodesian sample).

TABLE 2-2

Distribution of Fiber at the Termination of Exposure
(% of Total Deposited)[a,b]

Fiber	Nasal Passages	Esophagus	GI Tract	Lower Respiratory Tract
Chrysotile A	9 ± 3	2 ± 1	51 ± 9	38 ± 8
Chrysotile B	8 ± 2	2 ± 1	54 ± 5	36 ± 4
Amosite	6 ± 1	2 ± 1	57 ± 4	35 ± 5
Crocidolite	8 ± 3	2 ± 1	51 ± 9	39 ± 5
Anthophyllite	7 ± 2	2 ± 1	61 ± 8	30 ± 8
Fluoramphibole	3 ± 2	1 ± 1	67 ± 5	29 ± 4

[a]Source: Morgan et al., 1975

[b]Mean and SD

More recently, Barry et al. (1983) found chrysotile fibers in the alveolar macrophages, epithelium and interstitial perialveolar tissue of rats exposed to 9.06 mg chrysotile/m^3 for 7 hours. After 3 months of exposure for 7 hours/day, 5 days/week, numerous fibers and cellular changes were observed in the alveolar epithelium and interstitium.

Phagocytosis by macrophages was considered to be the major method by which chrysotile fibers inhaled by guinea pigs moved through the parenchyma of the lungs to the pleura. Macrophages that disintegrated before completing the journey discharged their contents in the lymphatic system (Holt, 1983).

In an *in vitro* study of the toxicity of several inhaled pollutants, three forms of UICC standard reference samples of asbestos fibers (amosite, crocidolite and Canadian chrysotile B) were seen by electron microscopy to be ingested by human bronchial epithelial cells (Haugen et al., 1982).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding toxicity associated with subchronic oral exposure to asbestos in humans could not be located in the available literature.

Jacobs et al. (1978) fed rats diets containing 0.5 or 50 mg of chrysotile daily for 14 months, and subsequently examined the GI tract by both light and electron microscopy. No effects were noted in the esophagus, stomach or cecum, but "structural changes in the villi of the ileum were quite evident at both dosage levels."

3.1.2. Inhalation. Only one study of subchronic inhalation exposure of humans to asbestos was located in the available literature. Harless et al. (1978) discovered airflow abnormalities (not further specified) in 17/23 individuals examined 1.5 and 8.0 months following an intense 5-month exposure to asbestos. Of the 17 affected individuals, 12 were nonsmokers or current light or ex-light smokers (<10 pack-years). The obstructive abnormalities were usually observed during measurements of 1-minute forced expiratory volume and of closing volume.

Male and female rats exposed to 9.06 mg chrysotile/m^3, 7 hours/day, 5 days/week for 3 months showed the presence of chrysotile fibers and considerable cellular change in the alveolar epithelial and interstitial cells (Barry et al., 1983). Most noteworthy was a 57% increase in the number of type II epithelial cells and a 90% increase in their average cellular volume. A 58% increase in the number of interstitial cells and a 40% increase in their average cellular volume were also observed. Infiltration

with macrophages accounted for nearly all the increase in interstitial cell numbers. Of cells that were observed to contain chrysotile fibers, 88% were macrophages. Eventually, calcification of these fibers occurred and cellular inclusions were thus formed.

Wagner (1963) exposed guinea pigs and vervet monkeys to chrysotile and amosite dust at concentrations of 37,600 or 30,000 particles/m^3, respectively, for 8 hours/day, 5 days/week for 49 weeks. The technique of asbestos analysis had the limitation of not being able to identify "long" asbestos fibers. Guinea pigs exposed to chrysotile developed pulmonary fibrosis, interstitial pneumonitis, cuboidal metaplasia of the epithelium of the alveolar ducts and cor pulmonale. Similar lesions but a more rapid onset were noted in guinea pigs exposed to amosite dust. Deaths occurred in monkeys exposed to chrysotile after 7, 10 and 22 months of exposure. Deaths of the first two were due to gastroenteritis. Deaths occurred in monkeys exposed to amosite after 4, 12 and 14 months of exposure. Pathological changes in both chrysotile- and amosite-exposed monkeys included lung fibrosis and cor pulmonale, histologically consistent with slight to moderate human asbestosis.

Subsequently, Wagner et al. (1974) exposed groups of ~20-25 Wistar rats to amosite, anthophyllite, crocidolite and chrysotile to establish a dose relationship between different asbestos dusts and pulmonary malignancies. Exposure was for 7 hours/day, 5 days/week for 3, 6, 12 or 24 months to air containing 10-11 mg/m^3. Overall, the severity of asbestosis (fibrosis, increased numbers of type II pneumocytes) correlated with increased length of exposure.

3.2. CHRONIC

Most studies of the chronic exposure of animals to asbestos by either the oral or inhalation route have been for the purpose of studying the ability of asbestos fibers to initiate a carcinogenic response. Therefore, most long-term studies of exposure to asbestos will be discussed in Chapter 4.

3.2.1. Oral. Bolton et al. (1982) fed margarine containing 5 mg UICC amosite, UICC crocidolite or UICC chrysotile A/g of margarine to groups of 23 HAN spf Wistar rats. Negative control and vehicle control rats (fed margarine without asbestos) were maintained. Margarine containing asbestos was fed ad libitum, and asbestos intake averaged ~250 mg/rat/week. Rats were treated for 25 months, and the majority were kept for the remainder of their lifespan.

The animals tolerated the experimental diets well. Rats given access to margarine with or without asbestos consumed ~30% less standard laboratory food and weighed consistently 25% more than rats not given access to margarine. The resultant obesity had no obvious effect on morbidity or mortality of the treated animals, with the majority surviving beyond 700 days of age. Light and electron microscopic examination of many tissues was performed. No penetration or damage to any of the gut tissues was observed. Although occasional asbestos fibers were found in several tissue residues, no lesions or effects of treatment were seen. Bolton et al. (1982) concluded that there were no significant adverse effects of prolonged asbestos ingestion in healthy laboratory rats.

3.2.2. Inhalation. In humans, a chronic, progressive pneumoconiosis (asbestosis) results from long-term inhalation of asbestos fibers. It is characterized by fibrosis of the lung parenchyma, which usually becomes radiographically discernible 10 years after the first exposure.

Radiographic lesions are usually small, irregular opacities, usually in the lower and middle lung fields. Pleural fibrosis and thickening, often with focal areas of calcification, are also found. Changes can occur more rapidly if exposure is more severe. Shortness of breath is the primary symptom, cough is somewhat less common, and signs such as rales, finger clubbing and weight loss occur in more advanced stages of the disease. The disease was first reported by Murray (1907), and has since been recognized frequently among occupationally-exposed workers.

It has been estimated that 50-80% of workers exposed to asbestos $\geq$20 years have radiographic evidence of asbestosis (Selikoff et al. 1965; Mount Sinai, 1976; Lewinsohn, 1972). In many cases, the disease progresses following cessation of exposure. In a group of workers employed in an asbestos factory for varying lengths of time between 1941 and 1954, radiographic changes were observed years after exposures as short as 1 week (Selikoff, n.d.).

Restrictive pulmonary dysfunction is also seen with asbestos exposure and may be accompanied by diffusional defects or airway obstruction (Bader et al., 1961). In the early stages of asbestosis there is little correlation between pulmonary function tests and radiographic changes; as the disease progresses, the degree of correlation between radiographic changes and pulmonary dysfunction increases markedly (Bader et al., 1961).

Families of asbestos-exposed workers can also be affected. Anderson et al. (1976) demonstrated that 36% of 626 family contacts of workers employed sometime between 1941 and 1954 at an asbestos insulation manufacturing facility had radiographic evidence of exposure to asbestos.

In addition to disease and disablement during life, asbestosis has accounted for a large proportion of deaths among exposed workers. Early investigators (Auribault, 1906; Murray, 1907) attributed the death of entire working groups to severe asbestosis. Since then, improvement in dust control has markedly reduced the incidence of mortality due to asbestosis, but workers in extremely dusty conditions, as in textile mills, stand a $\geq$40% probability of death because of asbestosis (Nicholson, 1976). From 5-20% of deaths may be attributed to asbestosis in groups of workers in occupations where dust is controlled more satisfactorily (Mount Sinai, 1976; Selikoff et al., 1979).

The BOHS (1968) estimated that exposure to airborne asbestos for <50 years at an air level of 2 fibers ($\geq$5 μm in length)/cm^3 would result in asbestosis in <1% of the exposed group. This estimate is based on the incidence of asbestosis as diagnosed by the presence of high-pitched rales in the basal portion of the lung field in a cohort of asbestos textile workers.

Gillam et al. (1976) indicated that gold miners exposed to a concentration of 0.25 amosite fibers (>5 μm in length)/cm^3 in air experienced an increase in deaths due to respiratory malignancies (10 observed vs. 2.7 expected, $p<0.005$) and respiratory nonmalignancies (8 observed vs. 3.2 expected, $p<0.05$). Simultaneous exposure to free silica dust also occurred, but reportedly at levels below OSHA (Code of Federal Regulations, 1981) standards, and these investigators (Gillam et al., 1976) concluded that the nonmalignant respiratory disease was caused primarily by asbestos, possibly assisted by low levels of silica dust.

The effects of chronic exposure of rats to asbestos fibers by inhalation was investigated by Reeves et al. (1974), who exposed 207 rats to 47.9-50.2 mg chrysotile, amosite or crocidolite/m^3 for 4 hours/day, 4 days/week for

2 years. Only 0.08-1.82% of the dusts retained fibrous morphology as assessed by light microscopy following completion of preparation procedures for dust generation. A marked histiocytic and giant cell response occurred in rats as a response to any of the forms of asbestos; pulmonary fibrosis and hyperplasia were most severe in the crocidolite-exposed group followed by the amosite-exposed group which was greater than the chrysotile-exposed group. These investigators also reported pulmonary fibrosis in mice, gerbils, rabbits and guinea pigs exposed to asbestos by the same protocol. Rats exposed to any of these asbestos dusts developed lung cancers and mesotheliomas.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the teratogenicity, fetotoxicity or effects on reproduction in humans or animals associated with either oral or inhalation exposure to asbestos could not be located in the available literature, although transplacental transfer of asbestos following oral exposure has been demonstrated (Pontefract and Cunningham, 1973; Cunningham and Pontefract, 1974).

3.4. TOXICANT INTERACTIONS

Asbestos exposure and cigarette smoking have been shown to act synergistically to produce dramatic increases in lung cancer over that from exposure to either agent alone. In a prospective study of 17,800 insulation workers exposed to asbestos, smoking histories were taken, and a 10-year observation period was begun (Hammond et al., 1979). Those insulation workers who claimed nonsmoker status experienced higher mortality (8) than expected (1.3) based on age-, calendar- and year-specific cancer rate data among smokers and nonsmokers compiled by the American Cancer Society. Insulation workers who reported being smokers experienced 268 deaths compared to 4.7

expected. These investigators concluded that exposure to asbestos appeared to multiply the risk of death by 4-6 times. The combination of exposure to asbestos and the habit of smoking increased the likelihood of death due to lung cancer by >50 times. In an earlier study, Selikoff et al. (1968) suggested that the risk of death from lung cancer in cigarette smoking asbestos workers was 92 times that of individuals exposed to neither pulmonary insult.

The study by Hammond et al. (1979) associated increased deaths from cancer of the larynx, pharynx, buccal cavity and esophagus among asbestos workers who smoked cigarettes. Among asbestos workers in this study, cancers of the pleura, peritoneum, stomach, colon and rectum were unrelated to smoking habits. Shettigara and Morgan (1975), however, found a much stronger association of laryngeal cancer with asbestos exposure rather than with cigarette smoking.

Berry et al. (1972) obtained retrospective smoking histories on a group of asbestos workers and evaluated the causes of mortality over a 10-year period. They concluded that the effects of cigarette smoking and exposure to asbestos were multiplicative rather than additive in increasing the incidence of lung cancers.

Some nonmalignant effects of asbestos also appear to be synergistically enhanced by cigarette smoking. Among a cohort of factory workers exposed to asbestos, Weiss (1971) found that radiographically-diagnosed fibrosis was increased in cigarette smokers compared to nonsmokers. Hammond et al. (1979) found that deaths due to asbestosis appeared to be increased in smokers compared with nonsmokers.

Simultaneous exposure to BaP and asbestos seems to provide convincing data that these two agents may act synergistically to produce malignant tumors. Pylev and Shabad (1973) reported that intratracheal injection of

6 mg chrysotile, upon which 0.144 mg BaP had been adsorbed, and 2 mg chrysotile simultaneously with 5 mg BaP resulted in malignancies in 29 and 54% of the treated rats, respectively. Administration of 6 mg chrysotile or 5 mg BaP alone yielded no tumors.

Miller et al. (1965) showed that intratracheal injection of chrysotile with BaP increased the tumor yield over that of BaP alone. In this study, amosite appeared to have little effect.

4. CARCINOGENICITY

4.1. HUMAN DATA

For an in-depth review of the literature the reader is referred to U.S. EPA (1985). The modern history of asbestos disease dates from the early 1900s when two reports documented uncontrolled dust conditions in asbestos textile factories. Murray (1907) described severe pulmonary fibrosis found at necropsy in a cohort of deceased workers who had worked 10-14 years in a carding room. Auribault (1906) discussed the deaths of 50 men in a short period (unspecified) following the opening of an asbestos weaving mill in France.

Two clinical reports associated lung cancer with exposure to asbestos (Lynch and Smith, 1935; Gloyne, 1935). Merewether (1947) clearly related lung cancer to asbestos exposure when he demonstrated that 13% of a group of asbestos workers, who had died of asbestosis, also had bronchogenic carcinomas. Mesothelioma, a rare tumor involving the pleura or peritoneum, was first described in an asbestos worker in 1953 (Weiss, 1953), was subsequently found to be frequently associated with exposure to asbestos (Wagner et al., 1960), and later, was unequivocally related to asbestos exposure (Newhouse and Thomson, 1965).

Gastrointestinal cancer was also found to be related to asbestos exposure among insulation workers (Selikoff et al., 1964), probably because a large fraction of inhaled asbestos is cleared from the respiratory tract and subsequently swallowed (see Section 2.2.). Gastrointestinal cancers may also result from ingestion of asbestos fibers in food or drinking water. In this document, the carcinogenicity of asbestos associated with inhalation will be considered separately from carcinogenicity associated with oral exposure, in spite of the fact that a substantial proportion of inhaled asbestos fibers are ultimately swallowed.

4.1.1. Oral. Historically, oral exposure of humans to asbestos fibers has been through the drinking water, resulting either from contact with asbestos deposits or transmission through asbestos cement water mains. Several studies of carcinogenicity in humans associated with asbestos in drinking water are summarized in Table 4-1.

Polissar et al. (1983) reported a slightly elevated incidence of pharyngeal and stomach cancers in males living in the Everett, WA, area, whose watershed is the Sultan River which reportedly contains unusually high asbestos levels (~200x10^6 fiber/ℓ). Since only males seemed to be affected, and since the population studied was small, these investigators concluded that the higher than expected incidence of stomach and pharyngeal cancer was probably not related to asbestos intake.

Harrington et al. (1978) and Meigs (1983) investigated the incidence of cancer of the GI tract and peritoneum related to asbestos in drinking water in several Connecticut communities, resulting from the use of asbestos cement pipe. No relationship was established between asbestos in the drinking water and the incidence of GI or peritoneal tumors.

The incidence of death due to cancer of the digestive tract or lungs, or tumors of all sites was elevated 16-49% in Duluth, MN residents compared with residents of other Minnesota cities. Duluth drinking water originates from Lake Superior, which is contaminated with fibrous tailings from iron-ore processing in the area. More recently, Sigurdson (1983) observed significant increases in deaths due to tumors of the peritoneum ($p<0.05$), GI tract ($p<0.01$) or prostate ($p<0.01$) in Duluth residents compared with residents of other Minnesota cities.

TABLE 4-1

Recent Studies of Cancers Related to Asbestos in Drinking Water

Watershed	Level of Exposure (fibers/ℓ)	Duration of Exposure (years)	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (positive)	Reference
Everett, Washington	~200x10⁶	23%; >30	GI tract	pharyngeal cancer (males)	NR	NR	p<0.05	Polissar et al., 1983
				stomach cancer (males)	NR	NR	p<0.05	
Various, Connecticut	"few hundred thousand"	<5 to >30	peritoneum	peritoneal mesothelioma	NR	NR	NS	Meigs, 1983
			GI tract	NR	NR	NS		
Escambia County, Florida	0.2-32.7x10⁶	NR	several	several	NR	NR	NS	Millette et al., 1983
Duluth, Minnesota	1-65x10⁶	NR	peritoneum	total tumors	4.3/100,000	1.4/100,000	p<0.05	Sigurdson, 1983
			GI tract	total tumors	2.8/100,000	0.3/100,000	p<0.01	
			prostate	total tumors	90.4/100,000	69.3/100,000	p<0.01	

NR = Not reported; NS = not significant

Cooper et al. (1978) reported on the incidence of death due to cancer in 721 census tracts of the five Bay Area counties in California associated with the chrysotile asbestos fiber concentrations in drinking water. Chrysotile content ranged from not detectable to 36×10^6 fibers/ℓ. By grouping population tracts according to a gradient of asbestos counts, statistically significant dose-related trends were noted for white males (lung and stomach cancer) and white females (gall bladder, esophageal and peritoneal cancer).

4.1.2. Inhalation. Many epidemiological studies have clearly implicated asbestos as a cause of bronchogenic cancers and pleural mesotheliomas in exposed workers (U.S. EPA, 1980b). The more significant epidemiological studies are summarized in Table 4-2.

Without exception, the incidence of deaths due to cancer is in excess of the expected cancer-associated death rates for large control populations. The occurrence of excess deaths due to cancer ranges from a low of 1.9 times the expected rate for lung cancers and pleural mesotheliomas in asbestos factory workers in England (Peto et al., 1977), to a high of 28 times the expected rate for lung and pleural cancers in women in asbestos textile manufacturing in England ($p<0.001$) (Newhouse et al., 1972).

Gillam et al. (1976) reported significant excess mortality from malignancies involving the respiratory tract in mine workers exposed to amosite at average concentrations of 4.82 fibers/cm^3. The observed number of deaths due to respiratory malignancies was 10/440, compared with an expected incidence of 2.7 ($p<0.01$).

A study of the incidence of mesothelioma and non-neoplastic lesions in a region of Turkey with very high environmental levels of naturally occurring asbestos was performed by Baris et al. (1979). The occurrence of 148 cases

TABLE 4-2

Epidemiological Studies: Human Cancers Associated with Inhalation of Asbestos

Size of Exposed Population	Site of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value)	Reference
165	Northern Ireland death rate	M	NR	5-50+ years	lower respiratory system	cancer	28	1.64	NR	Elmes and Simpson, 1971
557	death rates for England and Wales	F	severe	<2 years	lung and pleura	cancer	6	1.0	p<0.001	Newhouse et al., 1972
239		F	severe	<2 years	lung and pleura	cancer	14	0.5	p<0.001	
126		F	low to moderate	any exposure time	lung and pleura	cancer	2	0.3	p<0.05	
440	South Dakota general population	M	4.82 fibers/cm³	>60 months	respiratory system	malignant	10	2.7	p<0.01	Gillam et al., 1976
143	national death rates	M	10-15[a] fibers/cm³	≥20 years	lung	cancer	35[b]	4.54	p<0.001	Peto et al., 1977
963	national death rates	M/F	2.9-13.3[c] fibers/cm³	≥10 years	lung	cancer	36[b]	19.3	p<0.001	Peto et al., 1977
632	U.S. death rate data	M	NR	≥20 years	lung, stomach, colon, rectum	cancer cancer	42 29	6.02 9.71	NR NR	Selikoff et al., 1964
370	U.S. death rate data	M	NR	≥20 years	lung, stomach, colon, rectum	cancer cancer	47 14	6.18 3.92	NR NR	Selikoff, 1976

[a]Workers exposed prior to 1933. Exposure was estimated.

[b]Lung cancers and pleural mesotheliomas

[c]Workers exposed after 1933. Exposure measurements varied over the period measured. Actual measurements of asbestos dust were reported since 1951.

NR = Not reported

of malignant pleural mesothelioma (92 in males, 56 in females) was associated with the occurrence of asbestos fibers in the water, fields and streets of this region. In 1 year, 11/18 deaths were due to malignant pleural mesothelioma in a town of 604 inhabitants.

An extensive study by Selikoff et al. (1979) demonstrated the full spectrum of disease associated with asbestos exposure. The mortality experiences of a cohort of 17,800 United States and Canadian asbestos workers, which occurred over a 10-year period (1967-1976), were compared to those expected based on data compiled by the U.S. National Center for Health Statistics. Prior to 1940, these workers were exposed primarily to chrysotile, and subsequently, to a mixture of chrysotile and amosite. During this 10-year period, 2271 deaths occurred. The causes of these deaths as determined from death certificates or from "best evidence" (clinical, surgical, necropsy), and the expected incidences of deaths from these cancers, are detailed in Table 4-3.

Lung tumors were the most common cause of death and accounted for ~20% of the deaths. Pleural and peritoneal mesotheliomas, ordinarily rare enough so that expected deaths due to this cause have not been projected, accounted for ~8% of the 2271 deaths. Considerable discrepancy exists between the incidences of mesotheliomas as determined by "best evidence" compared with the incidence of mesotheliomas reported on death certificates. Selikoff et al. (1979) judged that diagnosis based on "best evidence" is more likely to be accurate, particularly in cases of rarely occurring tumors such as mesotheliomas. Cancers of the GI tract also appeared to be strongly associated with industrial exposure to asbestos.

In addition to the increase in lung cancers, mesotheliomas and GI cancers, recent case reports have associated exposure to asbestos with

TABLE 4-3

Deaths Among 17,800 Asbestos Insulation Workers
in the United States and Canada[a,b,c]
(January 1, 1967 - January 1, 1977)

Underlying Cause of Death	Expected	Observed		Ratio Observed/ Expected	
		BE[d]	DC[e]	BE[d]	DC[e]
Total deaths, all causes	1658.9	2271	2271	1.37	1.37
Total cancer, all sites	319.7	995	922	3.11	2.88
Cancer of lung	105.6	468	429	4.60	4.06
Pleural mesothelioma	NA[d]	63	25	NR	NR
Peritoneal mesothelioma	NA[d]	112	24	NR	NR
Mesothelioma	NA[d]	0	55	NR	NR
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of stomach	14.2	22	18	1.54	1.26
Cancer of colon-rectum	38.1	59	58	1.55	1.52
Cancer of larynx	4.7	11	9	2.34	1.91
Cancer of pharynx, buccal	10.1	21	16	2.08	1.59
Cancer of kidney	8.1	19	18	2.36	2.23
Deaths of less common malignant neoplasms					
Pancreas	17.5	23	49	1.32	2.81
Liver, biliary passages	7.2	5	19	0.70	2.65
Bladder	9.1	9	7	0.99	0.77
Testes	1.9	2	1	NR	NR
Prostate	20.4	30	28	1.47	1.37
Leukemia	13.1	15	15	1.15	1.15
Lymphoma	20.1	19	16	0.95	0.80
Skin	6.6	12	8	1.82	1.22
Brain	10.4	14	17	1.35	1.63
All other cancer	25.5	55	92	2.16	3.61

TABLE 4-3 (cont.)

Underlying Cause of Death	Expected	Observed		Ratio Observed/ Expected	
		BE[d]	DC[e]	BE[d]	DC[e]
Noninfectious pulmonary diseases total	59.0	212	188	3.59	3.19
Asbestosis	NA[d]	168	78	NR	NR
All other causes	1280.2	1064	1161	0.83	0.91

[a]Source: Adapted from Selikoff et al., 1979

[b]Expected deaths are based upon white male age-specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976.

[c]Man-Years of Observation: 166,853

[d]Rates are not available, but these have been rare causes of death in the general population.

BE = Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical)

DC = Number of deaths as recorded from death certificate information only

NA = Not available; NR = not reported

leukemia and myeloma (Kagan et al., 1979; Haidak et al., 1979; Rouhier et al., 1982). Kagan et al. (1979) and Haidak et al. (1979) reported cases of individuals with multiple myeloma and chronic lymphocytic leukemia concurrent with pulmonary asbestosis. A third patient with multiple myeloma developed a massive pleural mesothelioma (Kagan et al., 1979; Haidak et al., 1979). Another patient, who had been occupationally exposed to asbestos for 30 years, developed malignant alpha-chain disease, and was found to have malignant lymphoma (Rouhier et al., 1982). All of these cases showed lesions of asbestosis in addition to the diagnosed malignancies.

4.2. BIOASSAYS

4.2.1. Oral. Several studies of the carcinogenicity of asbestos administered orally to animals have been found in the available literature (Table 4-4). These data have severe limitations: the numbers in each experimental group were small; the doses of asbestos administered were limited; important information on experimental procedures is lacking; and systemic histopathological examinations were performed only on a few experimental animals.

Smith (1973) discounted the significance of a single neoplasm of the colonic mesentery in 1 of 45 hamsters fed a diet containing 1% chrysotile or amosite for an unspecified length of time because asbestos fibers were not found in sections of the tumor. The finding of asbestos fibers in tumor tissue seems unlikely, and, since mesenteric tumors in hamsters are rare, this result should not be disregarded arbitrarily.

The data summarized by Gross et al. (1974) were the results of unpublished studies from three laboratories over a 10-year period. Lack of information about experimental detail and lack of systemic histopathological examination of all treated animals renders interpretation of these limited data difficult.

TABLE 4-4

Summary of Experiments on the Effects of Oral Administration of Asbestos

Species/Strain	No./Sex	Material Administered	Dosage	Animals Examined for Tumors	Findings (malignant tumors)	Average Survival Time (days)	Reference
Rats/Wistar	25M, 25F	asbestos filter material containing 52.6% chrysotile	50 mg/kg bw/day in the diet for life	42	4 kidney carcinomas 3 reticulosarcomas 4 liver-cell carcinomas 1 lung carcinoma	441	Gibel et al., 1976
Rats/Wistar	25M, 25F	talc	50 mg/kg bw/day in the diet for life	45	3 liver-cell carcinomas	649	Gibel et al., 1976
Rats/Wistar	25M, 25F	control	control	49	2 liver-cell carcinomas	702	Gibel et al., 1976
Rats/Wistar SPF	32/NR	UICC Canadian chrysotile in malted milk powder	100 mg/day, 5 days/week for 100 days	32	1 gastric leiomyosarcoma	618	Wagner et al., 1977
Rats/Wistar SPF	32/NR	Italian talc	100 mg/day, 5 days/week for 100 days	32	1 gastric leiomyosarcoma	614	Wagner et al., 1977
Rats/Wistar SPF	16/NR	control	control	16	none	641	Wagner et al., 1977
Rats	10M	ball-milled chrysotile mixed with laboratory food	5% by weight of feed mix for 21 months	10	none	sacrificed	Gross et al., 1974
Rats "laboratory"	5/NR	control	control	5	none	sacrificed	Gross et al., 1974
Rats/Wistar SPF	31/NR	Rhodesian chrysotile 0.2%-0.4%	10 mg weekly for 16 weeks	31 less "a few"	2 mammary carcinomas	NR	Gross et al., 1974
Rats/Wistar SPF	33/NR	crocidolite in butter 0.2-0.4% mixture	5 mg weekly for for 16 weeks	33 less "a few"	none	NR	Gross et al., 1974
Rats/Wistar SPF	34/NR	crocidolite in butter 0.2-0.4% mixture	10 mg weekly for 16 weeks	34 less "a few"	1 lymphoma	NR	Gross et al., 1974
Rats/Wistar SPF	24/NR	control (butter)	control	(24?)	3 mammary carcinomas 1 thigh sarcoma	NR	Gross et al., 1974

TABLE 4-4 (cont.)

Species/Strain	No./Sex	Material Administered	Dosage	Animals Examined for Tumors	Findings (malignant tumors)	Average Survival Time (days)	Reference
Rats/Wistar SPF	35/NR	NW Cape crocidolite in butter (0.2-0.4%)	10 mg weekly for 18 weeks	35 less "a few"	none	NR	Gross et al., 1974
Rats/Wistar SPF	28/NR	Transvaal crocidolite in butter (0.2-0.4%)	10 mg weekly for for 18 weeks	28 less "a few"	none	NR	Gross et al., 1974
Rats/Wistar SPF	24/NR	control (butter)	control	(24?)	none	NR	Gross et al., 1974
Rats/Wistar	10M	1% chrysotile	in diet	7	2 kidney 1 peritoneal 1 lymphoma 1 fibrosarcoma 1 brain 1 pituitary	NR	Cunningham et al., 1977
Rats/Wistar	10M	control	NA	8	1 peritoneal fibrosarcoma	NR	Cunningham et al., 1977
Rats/Wistar	40M	1% chrysotile	in diet	36	3 thyroid 1 bone 1 liver 1 jugular body 2 leukemia/lymphoma 1 adrenal 1 large intestine anaplastic carcinoma 1 small intestine fibrosarcoma	NR	Cunningham et al., 1977
Rats/Wistar	40M	control	NA	38	1 thyroid 1 liver 2 adrenals 1 kidney nephroblastoma 1 leukemia/lymphoma 5 subcutaneous tissue	NR	Cunningham et al., 1977
Hamsters/NR	45/NR	chrysotile or amosite	1% in diet for unspecified period of time	45	1 mesenteric neoplasm*	NR	Smith, 1973

*From text, impossible to state whether tumor was benign or malignant.

NA = Not applicable; NR = not reported

Because of concern about the use of filter material containing asbestos in the purification of wine products, Gibel et al. (1976) fed rats diets containing asbestos filter material. Treatments continued throughout the natural lifespan of the animals; untreated controls were maintained. The finding of four malignant kidney tumors in treated rats is accorded particular significance in view of the finding of an elevated risk of kidney cancer among asbestos insulation workers (Selikoff et al., 1979) and a high excretion of asbestos in the urine of humans exposed to asbestos-contaminated drinking water (Cook and Olson, 1979). The presence of sulfated cellulose and condensation resin in the filter material complicates interpretation of these results.

Cunningham et al. (1977) fed diets containing 1% chrysotile to 10 male Wistar rats for up to 24 months. Control rats were maintained. In the treated group, seven malignancies were found, while in the 10 control rats only one malignancy was found. In a second trial, 40 treated and 40 control male Wistar rats were studied using the same experimental protocol. After 24 months of exposure, 11 malignancies were found in the treatment group and 11 malignancies were found in the control rats, which considerably reduces the apparent relevance of the large number of malignancies in the earlier study.

The U.S. EPA (1985) concluded a review of the available published animal data with the following statement:

> In animal populations, the majority of the experimental evidence suggests that chronic, high-level ingestion exposures to asbestos fibers failed to produce any definite, reproducible, organ-specific carcinogenic effect.

In addition to the published literature, U.S. EPA (1985) presents a summary of the data from a draft NTP (1984) report. In this study no evidence of carcinogenicity was found following feeding of short-range (98% <10 μm) chrysotile asbestos fibers to either male or female rats. In contrast, male rats ingesting intermediate-range chrysotile fibers (65% >10 μm with ~14% >100 μm) at a 1% dietary level showed an incidence of 3.6% for benign epithelial neoplasms in the large intestine. U.S. EPA (1985) quotes NTP (1984) as follows:

> Although not statistically significant (p=0.08) compared with concurrent controls (0/85), the incidence of these neoplasms was highly significant (p=0.003) when compared with the incidence of epithelial neoplasms (benign and malignant combined) of the large intestine in the pooled control groups (male) of all the NTP oral asbestos lifetime studies (3/524, 0.6%).

This study should be re-examined following peer review and final publication.

4.2.2. Inhalation. Several assays of the carcinogenicity of asbestos in laboratory animals exposed via inhalation have been conducted. Data from some of the more pertinent studies are summarized in Table 4-5.

Lynch et al. (1957) administered chrysotile dust (150-300x10^6 particles/ft^3, ~5297-10,595x10^6 particles/m^3) 8-12 hours/day, 5 days/week for 19 months to AxC F_1 mice. Although a higher incidence of pulmonary adenomas was reported in the exposed group (58/127) than in controls (80/222), these results were not statistically significant.

Exposure to 86 mg chrysotile dust/m^3 for 30 hours/week for 16 months resulted in lung tumors in 24/72 rats (Gross et al., 1967). No lung tumors were found in 39 control rats.

TABLE 4-5

Carcinogenicity of Asbestos in Animals Exposed by Inhalation

Species/ Strain	Sex	Dose/Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence	Reference
Mice $(AxC)/F_1$	M/F	150-300x10⁶[a] particles/ft³ (8-12 hours/day; 5 days/week)	19 months	19 months	92.6-98.8%[b]	dust	lung	adenoma	58/127 (NS)	Lynch et al., 1957
Mice $(AxC)/F_1$	M/F	untreated	NA	19 months	NA	untreated	lung	adenoma	80/222	Lynch et al., 1957
Rat/white	M	86 mg/m³[c]	62 weeks	≥16 months (lifetime)	milled	dust	lung and pleura	cancer	24/72[d]	Gross et al., 1967
Rat/white	M	0.0 mg	NA	lifetime	NA	untreated	lung	cancer	0/39	Gross et al., 1967
Rat/Charles River CD	M/F	48.6 mg/m³[e] (4 hours/day; 4 days/week)	24 months	24 months	NR	dust	lung and pleura	various	3/46	Reeves et al., 1974
Rat/Charles River CD	M/F	47.9 mg/m³[c] (4 hours/day; 4 days/week)	24 months	24 months	NR	dust	lung and pleura	various	3/43[v]	Reeves et al., 1974
Rat/Charles River CD	M/F	50.2 mg/m³[f] (4 hours/day;	24 months	24 months	NR	dust	lung and pleura	various	5/46[g]	Reeves et al., 1974
Rat/Charles River CD	M/F	0.0 mg/m³	24 months	24 months	NA	untreated	no tumors	NA	0/5	Reeves et al., 1974
Mouse/Swiss	M/F	48.6 mg/m³[e] (4 hours/day; 4 days/week)	24 months	24 months	NR	dust	no tumors	NA	0/17	Reeves et al., 1974
Mouse/Swiss	M/F	47.9 mg/m³[h] (4 hours/day; 4 days/week)	24 months	24 months	NR	dust	no tumors	NA	0/19	Reeves et al., 1974
Mouse/Swiss	M/F	50.2 mg/m³[f] (4 hours/day; 4 days/week)	24 months	24 months	NR	dust	bronchial	carcinoma	2/18	Reeves et al., 1974
Mouse/Swiss	M/F	0.0 mg/m³	24 months	24 months	NA	untreated	bronchial	carcinoma	1/6	Reeves et al., 1974

TABLE 4-5 (cont.)

Species/ Strain	Sex	Dose/Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence	Reference
Rat/ nonspecific	M/F	47.4-47.9 mg/m³[i] (4 hours/day; 4 days/week)	2 years	2 years	NR	dust	lung and pleura	various	3/54	Reeves, 1976
Rat/ nonspecific	M/F	48.2-48.6 mg/m³[j] (4 hours/day; 4 days/week)	2 years	2 years	NR	dust	lung and pleura	various	3/61	Reeves, 1976
Rat/ nonspecific	M/F	48.7-50.2 mg/m³[k] (4 hours/day; 4 days/week)	2 years	2 years	NR	dust	lung and pleura	various	7/50	Reeves, 1976
Rat/Wistar	M/F	14.1 mg/m³ 7 hours/day[e]	1 day	804 days	NR	dust	lung	various[l]	3/45	Wagner et al., 1974
Rat/Wistar	M/F	12.8 mg/m³ 7 hours/day[m]	1 day	806 days	NR	dust	lung	various[l]	2/44	Wagner et al., 1974
Rat/Wistar	M/F	12.5 mg/m³ 7 hours/day[f]	1 day	795 days	NR	dust	lung	various[l]	6/43	Wagner et al., 1974
Rat/Wistar	M/F	9.7 mg/m³ 7 hours/day[c]	1 day	763 days	NR	dust	lung	various[l]	1/42	Wagner et al., 1974
Rat/Wistar	M/F	14.7 mg/m³ 7 hours/day[n]	1 day	753 days	NR	dust	lung	various[l]	5/45	Wagner et al., 1974
Rat/Wistar	M/F	0.0 mg/m³ 7 hours/day	NA	803 days	NA	untreated	lung	adenoma	4/44	Wagner et al., 1974
Rat/Wistar	M/F	12.4 mg/m³ 7 hours/day 5 days/week[e]	3 months	771 days	NR	dust	lung	various[l]	10/37	Wagner et al., 1974
Rat/Wistar	M/F	13.5 mg/m³ 7 hours/day 5 days/week[m]	3 months	823 days	NR	dust	lung	various[l]	6/37	Wagner et al., 1974
Rat/Wistar	M/F	12.6 mg/m³ 7 hours/day 5 days/week[f]	3 months	817 days	NR	dust	lung	various[l]	14/36	Wagner et al., 1974
Rat/Wistar	M/F	12.1 mg/m³ 7 hours/day 5 days/week[c]	3 months	790 days	NR	dust	lung	various[l]	18/34	Wagner et al., 1974

TABLE 4-5 (cont.)

Species/ Strain	Sex	Dose/Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence	Reference
Rat/Wistar	M/F	12.3 mg/m³ 7 hours/day 5 days/week[n]	3 months	857 days	NR	dust	lung	various[l]	16/36	Wagner et al., 1974
Rat/Wistar	M/F	0.0 mg/m³	NA	793 days	NA	untreated	lung	adenoma	3/40	Wagner et al., 1974
Rat/Wistar	M/F	11.2 mg/m³ 7 hours/day 5 days/week[e]	6 months	763 days	NR	dust	lung	various[l]	2/18	Wagner et al., 1974
Rat/Wistar	M/F	10.9 mg/m³ 7 hours/day 5 days/week[m]	6 months	686 days	NR	dust	lung	various[l]	6/18	Wagner et al., 1974
Rat/Wistar	M/F	10.7 mg/m³ 7 hours/day 5 days/week[f]	6 months	788 days	NR	dust	lung	various[l]	4/18	Wagner et al., 1974
Rat/Wistar	M/F	10.2 mg/m³ 7 hours/day 5 days/week[c]	6 months	669 days	NR	dust	lung	various[l]	5/17	Wagner et al., 1974
Rat/Wistar	M/F	10.7 mg/m³ 7 hours/day 5 days/week[n]	6 months	766 days	NR	dust	lung	various[l]	8/19	Wagner et al., 1974
Rat/Wistar	M/F	10.8 mg/m³ 7 hours/day 5 days/week[e]	12 months	692 days	NR	dust	lung	various[l]	10/25	Wagner et al., 1974
Rat/Wistar	M/F	11.4 mg/m³ 7 hours/day 5 days/week[m]	12 months	759 days	NR	dust	lung	various[l]	20/28	Wagner et al., 1974
Rat/Wistar	M/F	10.6 mg/m³ 7 hours/day 5 days/week[f]	12 months	776 days	NR	dust	lung	various[l]	18/26	Wagner et al., 1974
Rat/Wistar	M/F	10.7 mg/m³ 7 hours/day 5 days/week[c]	12 months	778 days	NR	dust	lung	various[l]	11/23	Wagner et al., 1974
Rat/Wistar	M/F	10.9 mg/m³ 7 hours/day 5 days/week[n]	12 months	826 days	NR	dust	lung	various[l]	19/27	Wagner et al., 1974

TABLE 4-5 (cont.)

Species/ Strain	Sex	Dose/Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence	Reference
Rat/Wistar	M/F	10.6 mg/m³[a] 7 hours/day 5 days/week[e]	24 months	807 days	NR	dust	lung	various[l]	13/21	Wagner et al., 1974
Rat/Wistar	M/F	10.6 mg/m³ 7 hours/day 5 days/week[m]	24 months	778 days	NR	dust	lung	various[l]	16/18	Wagner et al., 1974
Rat/Wistar	M/F	10.3 mg/m³ 7 hours/day 5 days/week[f]	24 months	756 days	NR	dust	lung	various[l]	13/18	Wagner et al., 1974
Rat/Wistar	M/F	10.1 mg/m³ 7 hours/day 5 days/week[c]	24 months	585 days	NR	dust	lung	various[l]	10/21	Wagner et al., 1974
Rat/Wistar	M/F	10.1 mg/m³ 7 hours/day 5 days/week[n]	24 months	758 days	NR	dust	lung	various[l]	11/17	Wagner et al., 1974
Rat/Wistar	M/F	0.0 mg/m³	NA	754 days	NA	untreated	lung	various[l]	0/42	Wagner et al., 1974

[a] Chrysotile (very fine, low fiber content: Canadian)

[b] SiO_2 (37.12-43.36%), MgO (39.54-43.90%), H_2O (12-15%), FeO (0-6%), Fe_2O_3 (1-5%), Al_2O_3 (0.2-1.5%), CaO (0-0.3%). Pure chrysotile = $3MgO \cdot 2SiO_2 \cdot 2H_2O$

[c] Chrysotile (Canadian)

[d] Exclusive of lymphoblastomas, since this tumor type is known to occur spontaneously in those rats.

[e] Amosite

[f] Crocidolite

[g] 4 carcinomas of the lung; 1 adenocarcinoma of the lung

[h] Chrysotile

[i] Chrysotile - fiber count measured as 54 million fibers/m³

[j] Amosite - fiber count measured as 864 million fibers/m³

[k] Crocidolite - fiber count measured as 1105 million fibers/m³

[l] Adenoma, adenomatosis, adenocarcinoma, squamous carcinoma

[m] Anthophyllite

[n] Chrysotile (Rhodesian)

NR = Not reported; NA = not applicable; NS = not statistically significant

Reeves et al. (1974) tested the carcinogenicity of various forms of asbestos in rats, mice, rabbits, guinea pigs and gerbils. Dusts of chrysotile, crocidolite and amosite were prepared by ball-milling, a process noted for destroying much of the fibrous character of asbestos. Exposures were up to 24 months to air concentrations of 47.9-50.2 mg/m³. Fiber counts were 54 fibers/mℓ (chrysotile), 864 fibers/mℓ (amosite) and 1105 fibers/mℓ (crocidolite). Neoplasms were detected only in rats and mice. Rats exposed to crocidolite, chrysotile and amosite developed lung tumors in 5/46, 3/43 and 3/46, respectively. Papillary carcinomas developed in mice (2/18) exposed to crocidolite. Subsequently, Reeves (1976) exposed rats to chrysotile, crocidolite and amosite, using the protocol previously described for a 2-year treatment period. Fiber counts were as reported previously (Reeves et al., 1974). Crocidolite, with the highest fiber count, also induced the highest incidence of tumors (7/50), while chrysotile (3/54) and amosite (3/61) were associated with fewer tumors in treated animals.

Wagner et al. (1974) exposed CD Wistar rats to amosite, crocidolite, anthophyllite, Canadian chrysotile or Rhodesian chrysotile at concentrations of 9.7-14.7 mg/m³ for 1 day, 3, 6, 12 or 24 months for 7 hours/day, 5 days/week. Exposure to all forms of asbestos was associated with an increased incidence of lung carcinomas and mesotheliomas after 3 months of exposure. No mesotheliomas were found in rats exposed to Rhodesian chrysotile for any length of time.

4.3. OTHER RELEVANT DATA

Mutagenicity testing of chrysotile, amosite, anthophyllite or superfine chrysotile gave negative results in several strains (unspecified) of Escherichia coli and Salmonella typhimurium assay systems (Chamberlain and Tarmy, 1977). The authors recognized that since prokaryotic cells do not phagocytize particles as do eukaryotic cells, a positive response was not likely.

Sincock and Seabright (1975) reported finding chromosomal aberrations in CHO cells cultured in a medium containing 0.01 mg/mℓ of either chrysotile or crocidolite. In a more extensive series of experiments, both morphologic transformation and positive genetic responses resulted from the inclusion of several chrysotile or crocidolite samples in the culture medium of CHO cells (Sincock, 1977). Very fine glass fibers produced the same abnormalities, but chemically leached asbestos produced fewer abnormalities than did unleached asbestos.

4.4. WEIGHT OF EVIDENCE

Evidence indicates that ingested asbestos fibers may cause an excessive incidence of cancers of the GI tract. Polissar et al. (1983) found a slight but significant ($p<0.05$) increase in the incidence of pharyngeal and stomach cancers in males drinking asbestos-contaminated water from the Sultan River, considered to be one of the most highly contaminated water supplies in the country. Sigurdson (1983) reported a significant increase in the incidence of peritoneal tumors ($p<0.05$) and tumors of the GI tract ($p<0.01$) in residents of Duluth, MN, whose drinking water contained $1\text{-}65 \times 10^6$ fibers/ℓ.

Other investigators failed to find a positive association between ingested asbestos and cancer in humans. Harrington et al. (1978) and Meigs (1983) investigated the incidence of GI and peritoneal cancers in several Connecticut communities in which concrete-asbestos water mains are used. No relationship was established between asbestos in the drinking water and the incidence of these tumors.

Cooper et al. (1978) failed to find a dose-related trend in the incidence of cancer in 721 census tracts of five Bay Area counties of California by examining the mortality data and ranking the census tracts according to the level of asbestos in the drinking water.

Evidence for a carcinogenic role for asbestos in orally exposed animals is also not convincing. The data generated have severe limitations: the numbers of animals tested were small, the doses of asbestos used were limited, and systematic histopathological examination of all animals was not always performed. The most convincing data suggesting a carcinogenic role for orally-administered asbestos were provided in the study by Gibel et al. (1976), who fed rats diets containing asbestos filter material which is used to clarify wine products. The finding of four kidney carcinomas among 50 rats treated throughout their lifetimes was considered a significant finding in view of the fact that Selikoff et al. (1979) found an increased risk of kidney cancer associated with asbestos insulation workers. The presence of sulfated cellulose and condensation resin in the filter material fed to the test rats complicates interpretation of these results. Additional data are available in the form of a draft NTP (1984) report (see Section 4.2.1.).

The case for carcinogenicity of asbestos in humans exposed by inhalation is considerably more convincing. Many epidemological studies have demonstrated significant increases in the incidence of deaths due to cancer associated with inhalation (particularly occupational) exposure to asbestos (see Table 4-2). Peto et al. (1977) and Newhouse et al. (1972) have clearly shown that exposure to asbestos in the workplace is related to a significant ($p<0.001$) increase in the likelihood of death due to cancers of the lung and pleura. Gillam et al. (1976) associated malignancies of the lung with exposure to asbestos mining operations. Selikoff (1976) and Selikoff et al. (1964, 1979) have shown that working with asbestos insulation may dramatically elevate the likelihood of death due to cancer of the lung, pleura, peritoneum and GI tract.

The animal data substantiate the observation of cancers in humans associated with inhalation exposure to asbestos. Although several bioassays strongly suggest the carcinogenicity of inhaled asbestos fibers, the data of Wagner et al. (1974) best illustrate this phenomenon. This complex study, which employed five forms of asbestos and treatment times of from 1 day to 2 years followed by varied post-exposure times, is presented in tabular form in Section 4.2.2. This study did not present statistical analysis of the tumor incidence data.

In light of the sufficient evidence indicating carcinogenicity of asbestos in humans exposed by inhalation, which is well corroborated by the animal bioassay data, asbestos is most appropriately classifed as a Group A substance by application of the classification criteria devised by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984).

5. REGULATORY STANDARDS AND CRITERIA

The OSHA standard for asbestos fibers (defined as fibers >5 μm in length) in workplace air was set in 1972 at 5 fibers/cm³ TWA for an 8-hour day. In 1976, this standard was reduced to 2 fibers/cm³ for an 8-hour TWA. A ceiling concentration of 10 fibers/cm³ was set (Code of Federal Regulations, 1981).

The ACGIH (1980) recommended TWA-TLVs for asbestos as follows: amosite, 0.5 fiber/cm³; chrysotile, 2.0 fibers/cm³; crocidolite, 0.2 fiber/cm³; other forms, 2.0 fibers/cm³. In Great Britain, the BOHS (1968) also suggested a TWA of 2.0 fibers/cm³, although Peto (1978) suggested that exposure to this level may result in the death of 10% of workers exposed for a lifetime.

Standards for asbestos in foods or beverages could not be located in the available literature.

The U.S. EPA (1980b) has recommended criteria for ambient water based on estimated levels of asbestos that would result in increased lifetime cancer risks of 10^{-5}, 10^{-6} and 10^{-7} as 300,000, 30,000 and 3000 fibers, respectively. These criteria were derived from the association of GI cancer with occupational exposure to asbestos dusts and by applying several assumptions. Primary among these assumptions is that virtually all of the asbestos is ultimately swallowed, and is therefore capable of causing lesions, including neoplasms, in the GI tract. Estimates of occupational exposure levels were matched with observed incidence of death due to GI cancers from several epidemiological studies. A linear relationship between increased cancer risk and exposure level was also assumed.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Asbestos is a substance that is known to be carcinogenic. Although the U.S. EPA (1983c) determined that it is inappropriate to derive a potency factor for asbestos because its carcinogenic potency is related to specific fiber shapes, sizes and air concentrations, the U.S. EPA (1980b) estimated unit carcinogenic risks for asbestos based on human epidemological data. It is inappropriate, therefore, to consider an oral or inhalation AIS for asbestos.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Asbestos is a substance that is known to be carcinogenic. The U.S. EPA (1983c) determined that it is inappropriate to derive a potency factor for asbestos because its carcinogenic potency is related to specific fiber shapes, sizes and air concentrations.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. As reviewed in Section 4.1.1., oral exposure of humans to asbestos in drinking water has not been conclusively shown to result in increased risk of cancer. Polissar et al. (1983) associated an increased incidence of stomach and pharyngeal cancers with a high concentration of asbestos fibers in drinking water in the Everett, WA area. Epidemiologic evaluations of cancer incidence in residents of the five Bay Area counties of California (Cooper et al., 1978) indicated a dose-related trend in the incidence of lung and stomach cancer (males) and gall bladder, esophageal and peritoneal cancer (females). Other epidemiologic studies (Meigs, 1983; Millette et al., 1983) have failed to relate increased risk of cancer with exposure to asbestos.

Animal bioassays have not clearly established a carcinogenic role for asbestos administered by the oral route (see Section 4.1.2.).

The U.S. EPA (1980b) used human inhalation data to derive a risk estimate in order to develop ambient water quality criteria for asbestos. In a later evaluation, the U.S. EPA (1983c) suggested that it may not be appropriate to calculate a potency factor for asbestos because its carcinogenic potency is related to the size and shape of asbestos particles as well as its concentration in the air. This issue is currently undergoing review (U.S. EPA, 1985). The risk assessment portion of U.S. EPA (1985) is not as yet final. When completed, U.S. EPA (1985), as a more extensive evaluation of the asbestos issue, should supercede any recommendations in this document.

6.3.2. Inhalation. The carcinogenicity of asbestos for humans exposed by the inhalation route has been well established (Elmes and Simpson, 1971; Newhouse et al., 1972; Gillam et al., 1976; Peto et al., 1977; Selikoff et al., 1964, 1979; Selikoff, 1976).

Animal bioassays confirm the carcinogenicity of asbestos administered by inhalation (Gross et al., 1967; Reeves et al., 1974; Reeves, 1976; Wagner et al., 1974). According to U.S. EPA (1983c), it is inappropriate to derive a potency factor for asbestos because the carcinogenic potency of asbestos is related to specific fiber shapes, sizes and air concentrations.

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APPENDIX

Summary Table for Asbestos

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1*†	Reference
Inhalation				NA	
Oral				NA	

†Not appropriate to compute q_1* according to U.S. EPA (1983c) because carcinogenic potency is related to particle size, shape and concentration in air.

NA = Not available